Proteinuria, Hematuria and Glomerular Disease
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IRIM
July 15, 2012

Case
• 67 year old man - 4 week history of anorexia, nausea, lassitude, and pedal edema.
• Longstanding hypertension, well controlled with Lisinopril/hydrochlorothiazide.
• Type II DM x 5y controlled by diet
• Fenoprofen for osteoarthritis of the hip for the past 3 months.

Exam: BP 157/93mm, HR 72 bpm, JVP 8 cm; normal cardiac and pulmonary examinations; and 2+ pitting edema.
Urinalysis showed a specific gravity of 1.017, protein 4+, trace blood, and negative for glucose. Microscopic examination of the sediment showed 2-4 erythrocytes and and occasional granular casts.
Creat 1.0, 24h Urine with 7.7 gms, albumin 2.8g/dl. Serologies wnl
Ultrasound normal

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• The nephrotic-range proteinuria is most likely the result of:
  – A). Diabetic Nephropathy
  – B). Amyloidosis
  – C.) Systemic small vessel vasculitis
  – D.) Minimal change disease
  – E.) Hypertensive nephrosclerosis

Agenda
• Review of Renal Anatomy
  – (Vascular, Glomerular, Tubular)
• Proteinuria
  – Definitions and Measurement
  – Mechanisms; (Glomerular, Tubular, Overflow)
  – Management
• Hematuria
  – Renal vs Urologic
  – Evaluation
• Glomerular Disease
  – Nephrotic vs Nephritic Syndromes
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Definitions/Measurement

Total Protein or Albumin

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>Microalbuminuria</th>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Protein</td>
<td>&lt;150 mg/day</td>
<td>30-300 mg/day</td>
<td>&gt;300 mg/d</td>
</tr>
<tr>
<td>Protein/creat ratio</td>
<td>&lt;200 mg/g (&lt;0.2)</td>
<td>&gt;3.5</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt;30 mcg/mg</td>
<td>30-300 mcg/mg</td>
<td>&gt;300 mcg/mg</td>
</tr>
<tr>
<td>Albumin/creat ratio</td>
<td>&lt;30mcg/mg</td>
<td>30-300mcg/mg</td>
<td>&gt;300mcg/mg</td>
</tr>
</tbody>
</table>

Random Urines are Adequate!

Spot Urine Protein:Cr Concentration Ratio

Urine protein concentration varies throughout the day depending on hydration status:

[Prot]

0600  1200  1800  Midnight

Spot Urine Cr Concentration Ratio

Urine Cr concentration also varies throughout the day depending on hydration status:

[Cr]

0600  1200  1800  Midnight
Urine Protein:Cr Ratio

Average Creatinine Excretion/d = 1gm so UP/Creat~24h excretion in gms

Transient Proteinuria
- Usually 1+ on dipstick
- Absent on repeat determinations
  - 4% normal males
  - 7% normal females
  - Exercise, fever
  - 10% of pts during acute illness

Orthostatic Proteinuria
Proteinuria during ambulation or exercise that is absent when patient is in recumbent posture
- 2% to 5% or adolescents; rare > age 30
- Renal biopsy: 92% normal
- Hemodynamic alterations in kidneys with subtle glomerular structural abnormalities

Split urine collection:
- 16-hr ambulatory
- 8-hr recumbent < 50 mg protein

Proteinuria With Intrinsic Renal Disease

Nephrotic-Range Proteinuria
- > 3.5 g protein per day
  - Usually predominantly albumin and pathognomonic of glomerular disease
- Often associated with nephrotic syndrome:
  - Edema
  - Hypoalbuminemia
  - Hyperlipidemia
  - Hypercoagulable state

Nephrotic Syndrome
- Primary glomerular disease
- Secondary glomerular disease

Proteinuria With Intrinsic Renal Disease
- Glomerular
  - Leaky barrier
    - Isolated proteinuria
    - Nephrotic syndrome
  - Defective reabsorption (damage)
  - Overflow R/O Myeloma
- Tubular

Overflow R/O Myeloma
Nephrotic Syndrome: Primary Glomerular Diseases

Generally require renal biopsy for diagnosis:
- Focal, segmental glomerulosclerosis
- Membranous nephropathy
- Minimal change disease
- IgA nephropathy
- Membranoproliferative glomerulonephritis
- Fibrillary glomerulonephritis

Secondary Glomerular Diseases

- Diabetes mellitus
- Amyloidosis
- Infections
  - HBV, HCV, HIV, syphilis, schistosomiasis
- Autoimmune disease
  - SLE, RA
- Drugs
  - NSAIDs, gold, penicillamine,

Natural History of Diabetic Nephropathy

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Early DM</td>
<td>0-2</td>
</tr>
<tr>
<td>2</td>
<td>Structural Changes</td>
<td>2-5</td>
</tr>
<tr>
<td>3</td>
<td>Microalbuminuria</td>
<td>5-12</td>
</tr>
<tr>
<td>4</td>
<td>Overt Nephropathy</td>
<td>12-25</td>
</tr>
<tr>
<td>5</td>
<td>ESRD</td>
<td></td>
</tr>
</tbody>
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Tubular and Overflow Proteinuria

- Tubular Proteinuria; Typically <1.5g/day
  - Comprised of Tamm-Horsfall and β2-microglobulin
  - Can be seen with any cause of tubular injury; hypertension, ischemia, advanced renal failure
- Overflow: Filtered load exceed reabsorptive capacity: light chains

Important Pearl: urine microalbumin and dipstick will NOT detect light chains.

Management of the Proteinuric Patient

- Treatment of underlying cause when appropriate (steroids+)
- Treatment of hypertension (<130/80)
- Antiproteinuric therapy (RAS Inhibition)
- Dietary management (Na restriction)
- Lipid management (target LDL<100)
- Control of edema

Recommendations for RAS Inhibitors in Proteinuric Patients

- Rate of decline in renal function correlates with the level of proteinuria
- Titrate up to maximum tolerated dose (twice the anti-hypertensive dose)
- Follow proteinuria as a surrogate endpoint
- Discontinue other antihypertensive agents if necessary
- Control hyperkalemia with diet, diuretics and/or resins
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Hematuria: Definitions

- Urinalysis:
  - Microscopic – >2 rbcs/hpf
  - Gross – brown or red urine
  - Pigmented Sediment = Hematuria
  - Pigmented Supernatant = Myoglobin or Hemoglobin
- Renal vs Urologic: Urine Protein/Creat > 0.5 and/or abnormal UA

Hematuria with Intrinsic Renal Disease

- Vascular
  - Renal Artery Obstruction:
    - thrombosis, embolism, dissecting aneurysm, vasculitis
  - Renal Vein Obstruction:
    - thrombosis, compression
- Glomerular/Small Vessels
  - glomerulonephritis, vasculitis
  - HUS, TTP, DIC, Malignant HTN, SLE
- Tubular
  - interstitial nephritis; drugs, infection, immune

Urologic Evaluation

- Exclude: UTI, prostatitis, menses, exercise, stones
- Gross hematuria: if clots; urologic in origin
- Persistent hematuria (x3 or gross) associated with significant process in about 9% of patients
- Exclude urologic malignancy;
  - Cytology, CT scan, cystoscopy
- Hypercalciuria/uricosuria – 30-35% of children

Most common causes of renal hematuria without significant proteinuria:
- Thin basement membrane disease
- Alports syndrome
- IgA Nephropathy (wide spectrum; most common GN world wide)
  - gross hematuria common after mucosal infection

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Glomerular Disease

- Predominantly proteinuria; consider causes of nephrotic syndrome (>3.5 g/d + other)
- Nephritic syndrome: Azotemia, hypertension, active urinary sediment (casts, dysmorphic rbc's, wbc's), proteinuria (usually <1.5 g/d; can be nephrotic range)
  - Consider causes of acute glomerulonephritis (next slides)
- Often will overlap!

RPGN - Rapidly Progressive Glomerulonephritis:
- Anti-GBM, Goodpasture's
- Pauci-Immune, ANCA+ (Wegener's, PAN) Syndromes
- Immune Complex:
  - Low complement: MPGN Pattern of Injury - Post-Infectious, SLE, Cryos
  - Normal complement - IgA, HSP, Fibrillary

Mimickers:
- HUS/TTP, Malignant Hypertension, Scleroderma crisis, Emboli

Diagnostic Approach to Proteinuria

- Confirm proteinuria; exclude transient, orthostatic
- 24 hr protein excretion
  - < 3.5 g/day
  - > 3.5 g/day
- Hematuria
  - Yes: Check UPEP
  - No: Consider
- Reduced GFR
  - Yes: Check UPEP
  - No: Consider
- Proteinuria > 1 g/day
  - Yes: Check UPEP
  - No: Consider
- Clues to systemic disease, CKD
  - Yes: Check UPEP
  - No: Consider

Significant intrinsic renal disease

Nephritic-range proteinuria

Work-up for glomerular diseases

Diagnostic Approach to Hematuria

- Proteinuria > 0.5 g/d
- Dysmorphic RBCs; RBC casts
  - Yes
  - No
- Pyuria, WBC casts
  - Yes: Urine Cult, Urine Eos
  - No: Urine Cytology
- Blood cultures, ASLO
- Anti-GBM/ANCA
- C3, C4, ANA
- Hep B, C, HIV
- Cryoglobulins
- Kidney Biopsy
- Renal Imaging: US, CT
  - Pos: Further Evaluation
  - Neg: Cystoscopy
- Pos: Bx and Eval
  - Neg: Monitor

Case

Summary: 68 yo with HTN, DM, OA and subacute onset of nephrotic syndrome, no hematuria and preserved GFR

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The Most Appropriate Next Steps Would be to:
1. Admit for urgent renal biopsy and IV solumedrol
2. Await serologies and admit for biopsy if positive
3. Start RAS inhibitor and repeat labs in 1-2 weeks
4. Obtain renal cat scan and refer to Urology
5. Obtain 24h urine for calcium and uric acid excretion

A 37 yo attorney of Chinese descent presents with 1d of gross hematuria that has now resolved. He describes a moderately severe diarrheal illness several days ago but no fever or chills. His PMH is otherwise unremarkable. Family history is negative for renal disease and he does not use NSAIDs.

- Exam shows healthy appearing male in NAD, BP 136/82mmHg, Pulse 82, Afebrile Exam is within normal limits without rash or edema.
- Labs notable for serum creat 1.1mg/dl (baseline 1.0, 1 year ago at physical), UA with TNTC rbc, dysmorphic, UP/Creat ~2. Serologic workup is pending.

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This is IgA Nephropathy characterized by gross hematuria after mucosal infection. These patients do not necessarily need renal biopsy and control of proteinuria is important.

References